Published in final edited form as:

Sex Transm Dis. 2018 March ; 45(3): 147–151. doi:10.1097/OLQ.0000000000000723.

Neurosyphilis: Knowledge Gaps and Controversies

Susan Tuddenham and

Johns Hopkins University School of Medicine, Baltimore, MD

Khalil G Ghanem

Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

After reaching a nadir at the turn of the century, syphilis rates in the United States have increased since 2000. *T. pallidum* may disseminate to the central nervous system within hours to days after inoculation. In this review, we focus on knowledge gaps and areas of controversy in neurosyphilis epidemiology, diagnosis, and management. Modern estimates of the prevalence of neurosyphilis are hindered by the lack of consistent reporting data and are based on relatively small retrospective cohort studies. The various diagnostic modalities for neurosyphilis have significant limitations. While several novel biomarkers for neurosyphilis have been evaluated, none to date have found a place in clinical practice. The role of a cerebrospinal fluid examination in patients without neurological symptoms continues to be an area of controversy, while the data for the use of antibiotic regimens other than intravenous aqueous or intramuscular procaine penicillin for the treatment of neurosyphilis are limited. As syphilis incidence continues to increase unabated in many countries around the world, it is critical to address these gaps of knowledge.

Keywords

Syphilis; neurosyphilis; review; controversies

After reaching a nadir at the turn of the century, syphilis rates in the United States have increased steadily since then.[1] Neurologic manifestations of syphilis may occur during any stage of the infection. Animal models demonstrate that *T. pallidum* disseminates to the central nervous system within hours to days after inoculation.[2] While there have been several recent reviews on neurosyphilis,[3,4] our goal here is to focus on knowledge gaps and areas of controversy in the epidemiology, diagnosis, and management of neurosyphilis.

Epidemiology

Rates of neurosyphilis in the United States are not known. Syphilis is a reportable condition but reporting of neurosyphilis cases is inconsistent mainly because the surveillance definitions (see below) require data that are not often available. Much of what we know about the epidemiology of neurosyphilis predates the penicillin era. Early neurosyphilis,

Corresponding Author: Khalil Ghanem, JHUBMC, ID Division, 5200 Eastern Ave, MFL Center Tower, Suite 378, Baltimore, MD, 21224, Tel: 410-550-7905, Fax: 410-550-1169, kghanem1@jhmi.edu.

Conflicts of Interest: None

which manifests as meningeal or meningovascular involvement of the central nervous system, was rare. Merritt *et al.* identified only 80 cases of acute syphilitic meningitis from three hospitals over 15 years starting in 1920, and 37 cases amongst 2263 patients seen at Boston City Hospital (pp.10, 28).[5] What was clear, however, was that the incidence was strongly dependent on therapy. Early neurosyphilis was rare among persons who were not treated for syphilis (0.3%) but the incidence increased nearly ten-fold in those who were inadequately treated (2–3%) (p.358)[6]-suggesting that inadequate or incomplete treatment may alter the immune response in such a way as to increase the risk for early neurosyphilis (termed “neurorecurrence”). Merritt et al. reported that almost 30% of all patients with syphilis (including early stage syphilis) had neurosyphilis, though approximately 30% of these cases were classified as asymptomatic (p10)[5] (of note, among early neurosyphilis cases, Moore reported that 77% were asymptomatic).[7] Merritt et al. separately estimated that 3% (based on data from Mattauscheck and Pilcz, as well as their own data) to 15% (based on data from Moore) of patients infected with syphilis developed meningovascular manifestations (p.89).[5] Late neurosyphilis (or tertiary neurosyphilis) was more common. The Oslo Syphilis Study published in 1929 followed untreated patients with primary and secondary syphilis and reported that 9.5% developed late neurosyphilis.[8] Similar numbers were reported by Mattauschek and Pilcz in their 1913 study of 4134 cases of syphilis amongst Austrian army officers.[5,6,9] Merritt et al. estimated (based on data from others) that 5% developed general paresis (p.195), and (based on their own as well as data from others), 1.5–9% developed tabes dorsalis (p.243). [5]

After the introduction of penicillin in the 1940’s, cases of neurosyphilis decreased dramatically. In a retrospective study of all cases of neurosyphilis diagnosed and reported to the Danish centralized health system between 1971 and 1979, only 55 cases of neurosyphilis were identified, the majority of which likely represented persons who were reinfected following appropriate penicillin therapy.[10]

The onslaught of HIV corresponded with increasing numbers of reported neurosyphilis cases-particularly early neurosyphilis.[11–13] Whether this was the result of biological susceptibility as a consequence of immunosuppression or increased detection as a result of enhanced follow-up is not known. However, robust contemporary estimates of the prevalence of symptomatic neurosyphilis are lacking. Those that exist have largely been based on small retrospective studies of health department syphilis records, often in select populations. A CDC analysis of reported cases of neurosyphilis in HIV positive MSM in 4 US cities from 2002 to 2004 estimated the prevalence of early symptomatic neurosyphilis to be 1.7%,[12] while a review of syphilis cases diagnosed in Los Angeles amongst persons aged 19 to 65 in 2001–2004 estimated that 1.5% had confirmed or probable neurosyphilis.[14] A retrospective study of 238 HIV and syphilis co-infected patients from a large public hospital found that approximately 3% had neurosyphilis.[15] In a review of 573 syphilis cases in King County, WA from 2012–2013, 3.5% of cases met the study criteria of confirmed symptomatic neurosyphilis with abnormal CSF testing or an ophthalmologic examination consistent with ocular syphilis. A total of 7.9% had visual or hearing symptoms, which the authors suggest could have represented neurosyphilis.[16] Finally, a study in the Netherlands which examined countrywide hospital discharge diagnoses of neurosyphilis from a national registry as well as STI clinic syphilis diagnoses estimated that 10–13% of all cases of

syphilis diagnosed in that country from 1999–2010 had neurosyphilis. However this estimate was based on hospital discharge diagnoses rather than documented clinical examination or laboratory criteria.[17]

In summary, modern estimates of the prevalence of neurosyphilis are hindered by the lack of consistent reporting data and are based on relatively small retrospective cohort studies whose case definitions differ.

Diagnosis

Diagnostic Criteria

The diagnosis of neurosyphilis remains challenging as there are no gold standard tests. Consequently, the diagnosis is based on a combination of clinical and CSF findings. A potential source of confusion to the clinician is the dissonance between the Centers for Disease Control and Prevention's (CDC) surveillance definition of neurosyphilis,[18] and the clinical description of neurosyphilis found in the CDC STD Treatment Guidelines.[19] This is not surprising given that the goal of the surveillance document is primarily epidemiological while that of the latter is patient management. As a practical example, while the surveillance document does not take syphilis stage into consideration when defining neurosyphilis, the treatment document recognizes that a subset of patients with early syphilis may have asymptomatic CSF changes (including a positive CSF VDRL) that may not warrant additional diagnostic or therapeutic interventions.[19]

Neuroinvasion and Symptoms

The relationship between *T. pallidum* neuroinvasion and markers of neurosyphilis (i.e. neurological symptoms, pleocytosis, reactive CSF VDRL and treponemal antibody tests, and elevated CSF protein) is complex. One challenge are the limitations of the tests to detect neuroinvasion (i.e. rabbit infectivity test and CSF PCR). A landmark study by Lukehart et. al. demonstrated that 12 of 40 (30%) participants with early syphilis had evidence of neuroinvasion compared to 0 of 17 with latent syphilis (Lukehart's estimate of neuroinvasion in early syphilis is remarkably consistent with estimates from multiple investigators dating back to the early 1900s). While those with documented neuroinvasion appeared more likely to exhibit neurological symptoms (50% vs. 26%), CSF pleocytosis (64% vs.32%), elevated protein (50% vs. 21%), and reactive CSF VDRLs (33% vs. 14%), a significant number of participants with documented neuroinvasion did not exhibit these abnormalities. Surprisingly, neither HIV status nor reactive CSF treponemal antibodies appeared to be related to neuroinvasion.[20] While neuroinvasion may be transient, predictors of its persistence and the likelihood of resulting pathological changes are not well established.

A common question arises: Can a diagnosis of neurosyphilis be made in the presence of a normal CSF examination? While a normal CSF examination may be present in nearly 40% of persons with ocular syphilis[21] and over 90% of persons with otic syphilis,[22] a normal CSF (cells, protein, and serology) excludes most cases of neurosyphilis except (perhaps) for a subset of persons with tabes (two of 100 patients with tabes in Merritt's case series had a completely normal CSF, as well as negative blood serologies) (p.282).[5] It's worth noting that

Moore reported a broad array of symptoms in early syphilis ranging from mild ("neurosyphilis manifested by mild symptoms or slight physical signs, not of themselves diagnostic of central nervous system damage") to severe with increasing symptom severity reflected in more pronounced CSF abnormalities (p. 345).[6] This association between symptoms and CSF abnormalities was not observed in persons with late syphilis.

CSF VDRL

The lipoidal (or non-treponemal) test that is most commonly used to diagnose neurosyphilis from CSF is the VDRL. The test is thought to be highly specific in the absence of gross blood contamination.[3,23] CDC guidelines do not recommend use of the CSF RPR because of its lower sensitivity.[24,25] While there have been reports of false positive VDRLs in the CSF (e.g. with meningeal carcinomatosis, spinal cord tumor, trypanosomiasis, and cerebral malaria)[5,23,26], these occurred in patients without serological evidence of syphilis (in whom sending the CSF VDRL would not generally be appropriate). In practice, a reactive CSF VDRL is regarded as synonymous with a diagnosis of neurosyphilis. The sensitivity of the CSF VDRL, however, is still debated[3,27] because the lipoidal test that predated the VDRL, the CSF Wasserman, had a very high sensitivity for neurosyphilis: It was reactive in 86% of patients with early syphilitic meningitis (p.44)[5] and in all patients with paretic neurosyphilis (p. 383)[5], though 28% of patients with tabes dorsalis-particularly those with the later stages or "burned out" tabes-had a negative CSF Wasserman (p. 385).[5] It was even suggested that these numbers were underestimates as most of these cases occurred prior to the recognition of syndromes such as extracranial carotid artery disease, cerebral arteritis, basilar artery insufficiency, lacunar syndromes and viral meningoencephalitis, which may have accounted for some of the CSF abnormalities attributed to syphilis in persons with a nonreactive CSF Wasserman.[28,29] The current sensitivity estimate for the CSF VDRL is about 50–60%. The most frequently cited data for this estimate emanate from a large neurosyphilis case series published in 1972 by Hooshmand et al, involving 241 patients. Of the 176 patients who were tested, 43% had a nonreactive CSF VDRL, almost twice the number that had been previously reported to be nonreactive with the CSF Wasserman.[3,30] Not surprisingly, the case selection in the Hooshmand paper has been questioned, with experts suggesting that some of these patients may not have had neurosyphilis.[27,31s] It's worth noting that most papers published in the modern era have suggested a CSF VDRL sensitivity of 50–60%, [32,33s] but similar critiques could be leveled against these estimates. At the heart of this controversy is the lack of an alternative gold standard to make the diagnosis of neurosyphilis. While some experts have suggested that a clinical diagnosis of neurosyphilis always requires a reactive CSF VDRL,[27] it is unlikely that clinicians will withhold antibiotic therapy from patients with nonreactive CSF VDRLs if there is other compelling evidence for neurosyphilis (e.g. neurological symptoms with CSF pleocytosis and no alternate diagnosis).

CSF Treponemal Tests

The CSF treponemal antibody tests, in contrast, are felt to be relatively non-specific. Indeed, another critique of the Hooshmand paper was that it utilized the CSF FTA-ABS as a part of the criteria for the diagnosis of neurosyphilis.[31s] While nonspecific, the treponemal-specific antibodies in the CSF are thought to be highly sensitive. As per the CDC 2015 STD Treatment Guidelines, "Neurosyphilis is highly unlikely with a negative CSF FTA-ABS test,

especially among patients with nonspecific neurologic signs and symptoms."[19] What the guidelines suggest is that, in the absence of a test with 100% sensitivity, the negative predictive value depends on the pretest probability of the diagnosis. A systemic review of treponemal-specific CSF tests for neurosyphilis found considerable heterogeneity among studies with variations in reported sensitivities,[34s] a recent study found that the sensitivity for several different treponemal-specific tests ranged from 83.3% to 100%,[35s] and an additional study found similar results.[33s] The sensitivity of point of care CSF treponemal tests may be somewhat lower.[36s] Hence, in patients with serologic evidence of syphilis and a high clinical probability of neurosyphilis, a nonreactive CSF treponemal antibody test may not rule out neurosyphilis.[34,37s] These tests may be useful, however, to rule out the diagnosis of neurosyphilis when the pretest probability is moderate to low.

CSF Pleocytosis

In 1946, Merritt et al reported that of 80 cases of acute syphilitic meningitis, only 1 had a CSF analysis showing less than 10 white blood cells (WBC)/ml; 18% had a CSF with 11–50 WBC/ml (p.42).[5] In cerebral meningovascular syphilis, the cell count was less than 10 WBC/ml in 37% of cases, and 63% had greater than or equal to 10 WBC/ml (p.127).[5] In paretic neurosyphilis, 10% of patients had a normal cell count (p382).[5] In contrast, in tabetic neurosyphilis, 53% had CSF WBCs ranging from 0 to 5 cells/ml (p.385).[5] In a study by Marra et al., one of 8 patients with early syphilis diagnosed with definite neurosyphilis (positive CSF VDRL) had two WBC/ml in the CSF, as well as a normal protein.[38s] In Hooshmand's study, 18.4% had <5 WBC/ml in the CSF, but this series included a large number of patients with tertiary neurosyphilis.[30]

A cutoff of >5 cells/mL in the CSF has been a standard cutoff used to define CSF pleocytosis. CSF pleocytosis is not specific for diagnosing neurosyphilis because multiple conditions, both infectious and non-infectious, can lead to elevated WBC in the CSF.[39s] The interpretation of the CSF WBC is particularly problematic in persons infected with HIV, as a significant number may have CSF pleocytosis independent of neurosyphilis, particularly if they are not on antiretroviral therapy (ART).[40s] Though data are limited, it has been suggested that a cutoff of 10 cells/mL for HIV infected patients on ART and 20 cells/mL in those not on ART may improve specificity for a diagnosis of neurosyphilis.[41s] The CSF cell count appears to correlate with disease activity and is typically the first parameter to improve following therapy (p389).[5]

In summary, save for a subset of patients with tabes dorsalis, it is rare to encounter patients with neurosyphilis who lack CSF pleocytosis. As such, pleocytosis while non-specific is a sensitive marker for neurosyphilis.

Elevated CSF Protein

With the exception of some trace proteins and beta globulins, CSF proteins are derived from serum proteins. While CSF IgG is usually derived from plasma, local synthesis within the CNS does occur in a variety of disorders, including neurosyphilis. Elevated CSF protein is caused by increased permeability of the blood-CSF barrier or increased CSF protein synthesis in the CNS.[39s] As with CSF pleocytosis, elevated protein is non-specific and may

be found in a variety of infectious and non-infectious conditions.[39s] Therefore, a diagnosis of neurosyphilis based only on CSF protein elevation is highly non-specific. As for its sensitivity, Merritt et al found that 12% of patients with acute syphilitic meningitis (p.43), 25% of patients with general paresis (p.383), 34% of patients with cerebrovascular syphilis (p. 380) and 47% with tabes dorsalis had a CSF protein < 45 mg/dl (normal) (p.385).[5] In Hooshmand's study, 61% had a normal CSF protein, while in the study by Marra et al, 3 of 8 patients with definite neurosyphilis had a normal CSF protein.[30,38s] As such, CSF protein elevation is neither sensitive nor specific for making the diagnosis of neurosyphilis.

Several novel biomarkers for neurosyphilis have been evaluated.[42,43s] CSF CXCL13, for example, was found to have a sensitivity of 90% and a specificity of 37% for symptomatic neurosyphilis at a low cutoff value, while at a high cutoff value, it had a specificity of 79% and a sensitivity of 41% in HIV infected patients.[32] While this and other studies suggest that CXCL13 might provide some added value to existing CSF tests, particularly in HIV infected patients,[44s] none of the novel biomarkers to date have found a place in clinical practice. New and enhanced diagnostics for neurosyphilis are needed

Management

Currently, the CDC recommends that a CSF examination be performed in all persons with serological evidence of syphilis who have neurological signs and/or symptoms, and in asymptomatic persons with syphilis whose serological titers do not decline four-fold following stage-appropriate therapy.[19]

The Role of CSF Examination in Patients without Neurological Signs and/or Symptoms (with a Particular Focus on HIV-Infected Persons)

There has never been any controversy over the critical importance of CSF examinations in persons with neurologic signs and/or symptoms. However, while a significant proportion of asymptomatic patients with early syphilis have evidence of neuroinvasion and CSF abnormalities,[20,45s] there are no data to suggest that enhanced therapy beyond a single intramuscular 2.4 MU dose of benzathine penicillin G improves their long-term outcomes. In the pre-antibiotic era, the rationale was clear: experts advocated CSF examination in all patients regardless of symptoms because abnormal CSF examinations in persons with syphilis predicted poor long term neurological outcomes in asymptomatic patients.[3] Asymptomatic patients with a normal CSF examination were unlikely to develop long-term neurologic complications of syphilis unless their Wasserman titers increased.[46s] CSF abnormalities were less common in late syphilis, and asymptomatic patients with late syphilis and a normal CSF examination at 5 years were highly unlikely to develop tertiary complications.[46s]

Following the introduction of penicillin, the rates of neurosyphilis dramatically declined, and routine CSF examination in asymptomatic patients fell out of favor. The HIV epidemic re-ignited the debate over the need for CSF examination in asymptomatic patients, due to multiple reports of treatment failures in HIV-infected persons treated with CDC-recommended penicillin regimens. [47–49s] Patients with HIV and syphilis, particularly if their RPR titer is greater than or equal to 1:32, or they have a CD4 count less than or equal to 350

cells/mm^3, may be found to have CSF abnormalities consistent with asymptomatic neurosyphilis[4,50,51s] Most concerning, a small study by Lukehart et al. found that 2 out of 4 persons without neurologic symptoms who were found to have *T. pallidum* in their CSF failed to clear the organism after a single dose of 2.4 MU of BPG, and a third was deemed to have failed therapy based on persisting CSF abnormalities. All three patients who failed therapy were HIV positive.[20] However, the significance of asymptomatic neurosyphilis in the penicillin era, even in patients with HIV, remains unclear. No studies have followed untreated HIV-infected persons with asymptomatic neurosyphilis to see whether this predicts progression to symptomatic neurosyphilis. Such a study would be logistically and ethically problematic. Observational studies, in general, have not showed an increase in neurosyphilis cases among HIV-infected persons with early syphilis treated with a single dose of 2.4 MU of BPG, but the follow-up data for most of these studies were limited.[52,53s] A recent study in which a CSF examination was done an average of 8 months after treatment in 64 patients with HIV at high risk of neurosyphilis (RPR >=1:32 and/or CD4<350) treated with a single 2.4 MU dose of BPG found only one with asymptomatic neurosyphilis. No patients had developed symptomatic neurosyphilis.[54s]

In summary, there is insufficient evidence at present to suggest that identification of asymptomatic neurosyphilis in the antibiotic era helps to predict treatment failure even in patients with HIV. A randomized trial to determine whether a strategy of immediate lumbar puncture followed by therapy based on CSF results in better serological and functional outcomes in patients with syphilis who are at high risk for neuroinvasion is underway (ClinicalTrials.gov Identifier: NCT02031146).

The Role of CSF Examination in Persons whose Serological Titers Fail to Decline Appropriately following Stage-Directed Therapy

Patients who do not achieve a four-fold decline in nontreponemal serological titers within a specified period of time (12 months in early syphilis and 24 months in late syphilis) following appropriate stage-directed therapy are termed “serofast,” and the CDC recommends CSF examination in such persons. “Serofast” may also in some cases refer to patients who achieve a fourfold decline in non treponemal titer but do not completely revert from reactive to nonreactive.[55s] The CDC recommendation is based on pre-penicillin era data that suggest that up to 25% of persons with early syphilis who remain serofast (here the latter “serofast” definition applied) will progress to tertiary neurosyphilis.[6] There was, however, no association between the serofast state and progression to tertiary neurosyphilis in those with late latent syphilis. In the penicillin era, one case series from China did report on 17 HIV negative patients with secondary syphilis whose RPR titers declined fourfold but failed to revert to negative 24 months after treatment, who subsequently developed neurosyphilis. However, only four of these 17 patients had neurologic symptoms.[56s] Several studies have assessed short-term serological outcomes following re-treatment of serofast persons (i.e. those whose titers fail to decline four-fold following stage-appropriate therapy),[57,58s] but none have assessed long-term outcomes. Whether a CSF examination improves outcomes among asymptomatic persons who are serofast following stage-appropriate antibiotic therapy is not known.

The Role of Antibiotic Regimens Other than Aqueous Crystalline Penicillin or Procaine Penicillin in the Treatment of Neurosyphilis

Several small observational studies suggest that intravenous ceftriaxone for 10 to 14 days is a reasonable alternative regimen. [59–61s] Of interest, 3 weekly doses of 2.4 MU of BPG intramuscularly was a recommended treatment option for neurosyphilis through the 1982 CDC STD Treatment Guidelines.[62s] However, reports surfaced that these doses did not achieve consistent treponemicidal levels in the CSF.[63s] Despite decades of use for neurosyphilis, and good clinical responses, [64s] the recommendation to use 3 doses of 2.4 MU of BPG to treat neurosyphilis was ultimately abandoned. Whether treponemicidal concentrations in the CSF are needed to control neurosyphilis in patients with a robust immune system is not clear.

Summary

In summary, reliable estimates of the prevalence of neurosyphilis in the modern era are lacking and because there are no gold standard tests, and much of the data comes from the pre-antibiotic era, diagnosis of neurosyphilis is challenging and a source of controversy. Definitions of neurosyphilis differ between surveillance and clinical guidelines, which may lead to added confusion over management. The need for a CSF examination in asymptomatic patients is debated, though at present, there is insufficient evidence to suggest that the identification of asymptomatic neurosyphilis in the antibiotic era helps to predict treatment failure, even in patients with HIV. The management of serofast patients is controversial, and complicated by differing definitions. Finally, the efficacy of antibiotics other than IV penicillin in the treatment neurosyphilis is not well established.

In a preface to their seminal text entitled “Neurosyphilis,” published in 1946, Merritt, Adams and Solomon write, “Among the consequences of the syphilitic infection, involvement of the central nervous system stands first in frequency and gravity. Considering this fact, it may seem odd that our knowledge of syphilis of the nervous system has been of such slow growth. Even today many fundamental problems remain unresolved…”[5] More than 70 years later, critical knowledge gaps and important controversies remain in neurosyphilis epidemiology, diagnosis and treatment. As syphilis incidence continues to increase unabated in many countries around the world, it is critical, now more than ever, to address these.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

(For further references please see “Supplementary References”

1. CDC Sexually Transmitted Diseases Surveillance. 2015. https://www.cdc.gov/std/stats15/syphilis.htm
2. Collart P, Franceschini P, Durel P. Experimental rabbit syphilis. The British journal of venereal diseases. 1971; 47(6):389–400. [PubMed: 5160160]

3. Ghanem KG. REVIEW: Neurosyphilis: A historical perspective and review. CNS neuroscience & therapeutics. 2010; 16(5):e157–168. [PubMed: 20626434]
4. Marra CM. Neurosyphilis. Continuum. 2015; 21:1714–1728. (6 Neuroinfectious Disease). [PubMed: 26633785]
5. Merritt, A., Solomon. Neurosyphilis. Oxford University Press; 1946.
6. Moore, J. The Modern Treatment of Syphilis. Baltimore, MD: 1943.
7. Moore JE. Studies in Asymptomatic Neurosyphilis: The Classification, Treatment, and Prognosis of Early Asymptomatic Neurosyphilis. II. Bulletin of the Johns Hopkins Hospital. 1922; 33(377):231–246.
8. Clark EG, Danbolt N. The Oslo study of the natural history of untreated syphilis; an epidemiologic investigation based on a restudy of the Boeck-Bruusgaard material; a review and appraisal. Journal of chronic diseases. 1955; 2(3):311–344. [PubMed: 13252075]
9. Mattauscheck E, Pilcz A. Zweite Mitteilung uber 4134 katamnestisch verfolgte Falle von luetischer Infektion. Ztschrfdges Neurol u Psychiat. 1913; 15(608)
10. Perdrup A, Jorgensen BB, Pedersen NS. The profile of neurosyphilis in Denmark A clinical and serological study of all patients in Denmark with neurosyphilis disclosed in the years 1971–1979 incl. by Wassermann reaction (CWRM) in the cerebrospinal fluid. Acta dermato-venereologica Supplementum. 1981; 96:1–14. [PubMed: 6953720]
11. Centers for Disease C, Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men--four cities, United States, January 2002-June 2004. MMWR. Morbidity and mortality weekly report. 2007; 56(25):625–628. [PubMed: 17597693]
12. Flood JM, Weinstock HS, Guroy ME, et al. Neurosyphilis during the AIDS epidemic, San Francisco, 1985–1992. The Journal of infectious diseases. 1998; 177(4):931–940. [PubMed: 9534965]
13. Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. Aids. 2008; 22(10):1145–1151. [PubMed: 18525260]
14. Taylor MM, Aynalem G, Olea LM, et al. A consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001–2004. Sexually transmitted diseases. 2008; 35(5):430–434. [PubMed: 18446083]
15. Brandon WR, Boulos LM, Morse A. Determining the prevalence of neurosyphilis in a cohort co-infected with HIV. International journal of STD & AIDS. 1993; 4(2):99–101. [PubMed: 8476973]
16. Dombrowski JC, Pedersen R, Marra CM, et al. Prevalence Estimates of Complicated Syphilis. Sexually transmitted diseases. 2015; 42(12):702–704. [PubMed: 26562700]
17. Daey Ouwens IM, Koedijk FD, Fiolet AT, et al. Neurosyphilis in the mixed urban-rural community of the Netherlands. Acta neuropsychiatrica. 2014; 26(3):186–192. [PubMed: 25142195]
18. Centers for Disease C. National Notifiable Diseases Surveillance System (NNDSS). Syphilis 2014 Case Definition. 2014.
19. Workowski KA, Bolan GA, et al. Centers for Disease C. Sexually transmitted diseases treatment guidelines, 2015. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports. 2015; 64(RR-03):1–137.
20. Lukehart SA, Hook EW 3rd, Baker-Zander SA, et al. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. Annals of internal medicine. 1988; 109(11):855–862. [PubMed: 3056164]
21. Balaskas K, Sergentanis TN, Giulieri S, et al. Analysis of significant factors influencing visual acuity in ocular syphilis. The British journal of ophthalmology. 2011; 95(11):1568–1572. [PubMed: 21398411]
22. Yimtae K, Srirompotong S, Lertsukprasert K. Otosyphilis: a review of 85 cases. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007; 136(1):67–71. [PubMed: 17210336]
23. Madiedo G, Ho KC, Walsh P. False-positive VDRL and FTA in cerebrospinal fluid. Jama. 1980; 244(7):688–689. [PubMed: 6993717]
24. Marra CM, Tantalo LC, Maxwell CL, et al. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sexually transmitted diseases. 2012; 39(6):453–457. [PubMed: 22592831]

25. Zhu L, Gu X, Peng RR, et al. Comparison of the cerebrospinal fluid (CSF) toluidine red unheated serum test and the CSF rapid plasma reagin test with the CSF venereal disease research laboratory test for diagnosis of neurosyphilis among HIV-negative syphilis patients in China. Journal of clinical microbiology. 2014; 52(3):736–740. [PubMed: 24335955]
26. Delaney P. False positive serology in cerebrospinal fluid associated with a spinal cord tumor. Neurology. 1976; 26(6 PT 1):591–593. [PubMed: 945503]
27. Musher DM. Editorial Commentary: Polymerase Chain Reaction for the tpp47 Gene: A New Test for Neurosyphilis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016; 63(9):1187–1188. [PubMed: 27585980]
28. Simon RP. Neurosyphilis. Archives of neurology. 1985; 42(6):606–613. [PubMed: 3890813]
29. Jordan KG. Modern neurosyphilis--a critical analysis. The Western journal of medicine. 1988; 149(1):47–57. [PubMed: 3043897]
30. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. Jama. 1972; 219(6):726–729. [PubMed: 5066697]